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A Look on the Effects of Treatment Noncompliance in the Multivariate CACE Analysis via Bayesian Approach

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Abstract

The *Complier Average Causal Effect* (*CACE*) is a methodology that is popular in estimating the impact of an intervention among treatment even when there is noncompliance. Treatment noncompliance is a common issue in *RCTs* that may plague the randomization settings and may produce treatment effect estimates that are biased. Yue Ma in 2018 introduced the *Multivariate CACE* (*MCACE*) analysis and showed that the methodology outperformed the classical *CACE* methodology via the maximum likelihood estimation (*MLE*) approach [9].

This paper explores the behavior of the model treatment estimates for *MCACE* model via a *Bayesian* Estimation (*BayesE*) approach. The proposed *BayesE* methodology explores impact on the treatment effect parameters when varied values of compliance rates ρ_c are imposed. Here, $\rho_c \in \{20\%, 50\%, 80\%\}$ and a ρ_c of 20% implies an 80% noncompliance. The derived *MCACE* models are then compared to the derived *MCACE* models using *MLE*.

Simulation study shows that as ρ_c increases from 20% to 80%, the derived treatment effect estimates of the *MCACE* model via *BayesE* gave more accurate and more precise values than the treatment effect estimates derived via *MLE*. Comparison of the two models is based on its corresponding variances of the estimates and its mean squared error (*MSE*) values.

1 Introduction

Noncompliance is an important issue in the design and conduct of randomized controlled trials (*RCTs*) - a type of study in which subjects are randomly assigned to either a treatment group receiving some clinical intervention or a control group. Treatment noncompliance arises when participants do not receive the treatment or the intervention to which they were randomly assigned or allocated [5]. Most often, noncompliance occurs when human subjects are involved in the randomized experiments, say for example, participants may refuse to take the treatment

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due to side effects or because of inconvenience of the compliance procedure. To this effect, noncompliance turns out to be an important issue as it may lead to biased estimates of the actual treatment effect when doing parameter estimation of a model [6].

Two traditional approaches in estimating the treatment effect parameter are the intention–to–treat (ITT) analysis and the as–treated (AT) analysis [4]. However, both analyses tend to offer conservative estimate of the actual treatment effect under noncompliance, thus is biased for method effectiveness. In [8], the *Complier Average Causal Effect* ($CACE$) Analysis was introduced as an alternative methodology for estimating the method effectiveness. The $CACE$ is a particular form of the ITT analysis or the AT analysis where inference concerns on the average treatment effect within the subgroup of compliers.

In the effort to better evaluate the treatment efficacy in RCT studies, many researchers take multiple measurements, thus producing multivariate outcomes. Thus, the *univariate CACE* ($uCACE$) model evolved to a procedure called the *multiple univariate CACE* ($muCACE$) model to cater the case of dataset with multivariate outcomes to evaluate the treatment effect. But when the $muCACE$ analysis is performed on k-dimensional outcomes separately, $muCACE$ models fail to capture the potential correlations among multivariate outcomes. For a given population, however, the compliance behavior depends on baseline variables rather than the type of outcomes; that is, there should be only one compliance rate for one population.

To this effect, the $MCACE$ model was studied by [9] and found out that the methodology will outperform the $muCACE$ models in three ways. Firstly, the $CACE$ model considers the compliance mechanism of the data set. In general, the compliance rate is not fully observable in $RCTs$, thus needs to be estimated from the observed outcomes and baseline covariates. Secondly, the $muCACE$ model fails to capture the potential correlations among multivariate outcomes. In many situations, we are not sure about the underlying correlations among outcomes, thus performing multiple univariate analysis may risk losing information about the given data. Lastly, the significance of treatment effect is of great interest to researchers in many, if not all, RCT studies. Multiple univariate tests inflate both the experiment-wise type I error rate and the experiment-wise type II error rate when there are more than one dependent measurements.

In [3], the $muCACE$ model is used to analyze multivariate outcomes and showed that $muCACE$ estimates provide greater difference in change scores from baseline compared to the conservative ITT approach. Both procedures arrived at the same conclusion that the treatment effect was statistically significant. However, it was observed that the dataset has some noncompliance issues. For example, nearly half of the participants in the treatment group failed to adhere to their original assignment. In this scenario, the $muCACE$ models failed to capture the noncompliance effect and its potential correlations among multivariate outcomes.

In the attempt to overcome the disadvantages of the $muCACE$ model, [9] introduced the *Multivariate CACE* ($MCACE$) analysis and showed that the procedure can capture the potential correlations among multivariate outcomes, generate interpretable results, and boost the confidence of the test results. In this research work, estimates were derived via the *Maximum Likelihood Estimation* (MLE). However, [7] clarified that statistical issues in conducting randomized trials includes the choice of a sample size. The sample size is determined whenever a trial is stopped early, and the appropriate analysis and interpretation of the trial is conducted. In this regard, having a prior information can contribute to the efficiency of the derived estimates and thus, using a *Bayesian* estimation approach may be an advantage. It was pointed out in [7] that the *Bayesian* estimation approach allows a formal basis for using external evidence and in addition provides a rational way for dealing with issues such as the ethics of randomization, trials to show treatment equivalence, the monitoring of accumulating data and the prediction of the consequences of continuing a study.

No attempt has been made to consider the *Bayesian* approach in estimating the treatment effect parameter using the *MCACE* models which may be practical in real-world situation. It is in this direction that this paper aims to explore. Thus, this paper mainly focuses on the *MCACE* analysis via *Bayesian* estimation approach labeled as *BayesE*. Investigation centers in estimating the treatment effect parameter for multivariate outcomes at a fixed sample size n and effect size δ_c while varying the compliance rate (say, $\rho_c \in \{20\%, 50\%, 80\%\}$). Accuracy and precision of the derived treatment effect estimates using both *BayesE* and *MLE* procedures are then compared.

2 The Proposed Methodology

2.1 Multivariate CACE Procedure

The *CACE* procedure is also known as the *Local Average Treatment Effect* (*LATE*) procedure in Economics literature [9]. The *Complier Average Causal Effect* (*CACE*) is a particular form of the *ITT* analysis or the *AT* analysis where inference concerns the average treatment effect within the subgroup of compliers. The *Complier Average Causal Effect* (*CACE*) model is defined as follows:

Let D be a new treatment on some health outcome Y in a population of N participants. The initial assignment of participants is stored in the variable X where,

$$X_i = \begin{cases} 1 & \text{if the } i\text{th participant is assigned to the treatment} \\ 0 & \text{if the } i\text{th participant is assigned to the control.} \end{cases}$$

The actual receipt of the treatment is denoted by Z where,

$$Z_i = \begin{cases} 1 & \text{if the } i\text{th participant receives the treatment} \\ 0 & \text{if the } i\text{th participant does not receive the treatment.} \end{cases}$$

For clinical trials involving human subjects, the value of the binary variable Z is not under researchers' control due to a number of ethical problems. Thus, Z is written as a function of X, that is, $Z_i(X)$ is an indicator function of whether the ith participant takes the treatment given assignment X or not, that is,

$$Z_i(X) = \begin{cases} 1 & \text{if the } i\text{th participant receives the treatment given assignment X} \\ 0 & \text{if the } i\text{th participant does not receive the treatment given assignment X.} \end{cases}$$

In the case of perfect compliance, $Z_i(X) = X$ for all participants. Unfortunately, $Z_i(X)$ differs from X_i for various reasons in practice. Similarly, $Y_i(X, Z_i(X))$ can be defined as the outcome of the ith participant given the random assignment X and the actual receipt Z. For multivariate analysis, $Y(X, Z)$ is an $N \times k$ matrix. Define $Z_i = (Z_i(0), Z_i(1))$ and $Y_i = (Y_i(0, Z_i(0)), Y_i(1, Z_i(1)))$ to be the potential outcomes, which can be partially observed in the experiment. Hence, the compliance type can take four possible values given by:

$$Z_i(X) = \begin{cases} c \text{ (complier)} & \text{if } Z_i(X) = X & \text{for } X = 0, 1 \\ n \text{ (never-taker)} & \text{if } Z_i(X) = 0 & \text{for } X = 0, 1 \\ a \text{ (always-taker)} & \text{if } Z_i(X) = 1 & \text{for } X = 0, 1 \\ d \text{ (defier)} & \text{if } Z_i(X) = 1 - X & \text{for } X = 0, 1. \end{cases}$$

Next, let C be a vector with N elements and N_t be the number of participants of type t, where $t \in \{c, n, a, d\}$ with c as complier, n as never-taker, a as always-taker and d as defier. The ITT effect on Y can be written as:

$$IIT_Y = \sum_{t \in \{c,n,a,d\}} \frac{N_t \; ITT_Y^{(t)}}{N}$$

and for $t \in \{c, n, a, d\}$, the ITT effect on Y for each compliance type can be written as:

$$ITT_Y^{(t)} = \sum_{\{i|C_i=t\}} \frac{Y_i(1, Z_i(1)) - Y_i(0, Z_i(0))}{N_t}. \tag{1}$$

Next, define the $CACE$ of Z on Y to be $ITT_Y^{(C)}$. For compliers, $Z_i(1) = 1$ and $Z_i(0) = 0$ and by the weak exclusion restriction assumption, Equation (1) can be simplified as:

$$CACE = ITT_Y^{(t)} = \sum_{\{i|C_i=C\}} \frac{Y_i(1) - Y_i(0)}{N_C} \tag{2}$$

where, N_C is the total number of compliers in treatment group and control group. Under the weak exclusion restriction assumption, the subgroup of never-takers does not address the causal effect of receiving the new treatment since both $Y_i(1, Z_i(1))$ and $Y_i(0, Z_i(0))$ represent outcomes without taking any treatment. Therefore, $ITT_Y^{(n)} = 0$.

To extend the $uCACE$ model to multivariate cases, assume that the health outcome Y follows a multivariate normal distribution, that is, for compliers in the treatment group, let

$$Y_{(t)} \sim MVN_k(\mu_k + \delta_c, \Sigma_c),$$

for compliers in the control group,

$$Y_{(c)} \sim MVN_k(\mu_c, \Sigma_c);$$

and for noncompliers,

$$Y_{(n)} \sim MVN_k(\mu_n, \Sigma_n);$$

where MVK_k denotes the k-dimensional normal distribution and Y is the multivariate response or outcome. In the multivariate case, μ_c, δ_c and Σ_c denote the mean, the treatment effect size and the variance-covariance matrix for the compliers, respectively, and μ_n, δ_n and Σ_n are the mean, the treatment effect size and the variance-covariance matrix for the noncompliers. With the assumption that the response or outcome Y follows a multivariate normal distribution, Equation (2) becomes,

$$MCACE = ITT_{Y_1,Y_2,\ldots,Y_n}^{(C)} = \sum_{\{i|C_i=C\}} \frac{Y_i(1) - Y_i(0)}{N_C}. \tag{3}$$

2.2 Bayesian Estimation

In *Bayesian* statistics, the conjugate prior of the mean vector is another multivariate normal distribution [2]. Also, assumptions are specified mathematically as prior distributions. Data are represented through a likelihood model. *Bayes' Rule* combines prior distribution and data likelihood into a posterior distribution. A formal expression of the Bayes' Rule is as follows;

$$p(\theta|y, x) = \frac{p(\theta)p(y|\theta, x)}{p(y)}$$

where θ is the estimated parameter. In the context of an *RCT*, θ is the effect of the treatment x on dependent variable y. Moreover, $p(\theta)$ is the prior distribution of the treatment effect, which captures the researcher's beliefs about the model parameter prior to any analysis. Also, $p(y|\theta, x)$ is the likelihood function and is the probability of the observed data given the parameter. Further, $p(y)$ is a normalizing constant with respect to θ that ensures the left-hand side $p(\theta|y, x)$ is a proper probability distribution that integrates to 1.

For some purposes and simplicity, the denominator can be ignored and one can rewrite the expression for the posterior $p(\theta|y, x)$ as;

$$p(\theta|y, x) = p(\theta)p(y|\theta, x).$$

The posterior distribution is then proportional to the product of the prior and the likelihood. Ultimately, the goal of modeling is to learn the posterior distribution $p(\theta|y, x)$ and summarize it accurately [1].

Figure 1 shows how the proposed methodology in this study is applied with multivariate simulated data. The *MCACE* model building with specified parameters, both via *Maximum Likelihood Estimation* (*MLE*) and *Bayesian Estimation* (*BayesE*) are generated using the mvnmle and MVNBayesian packages in the R software, respectively.

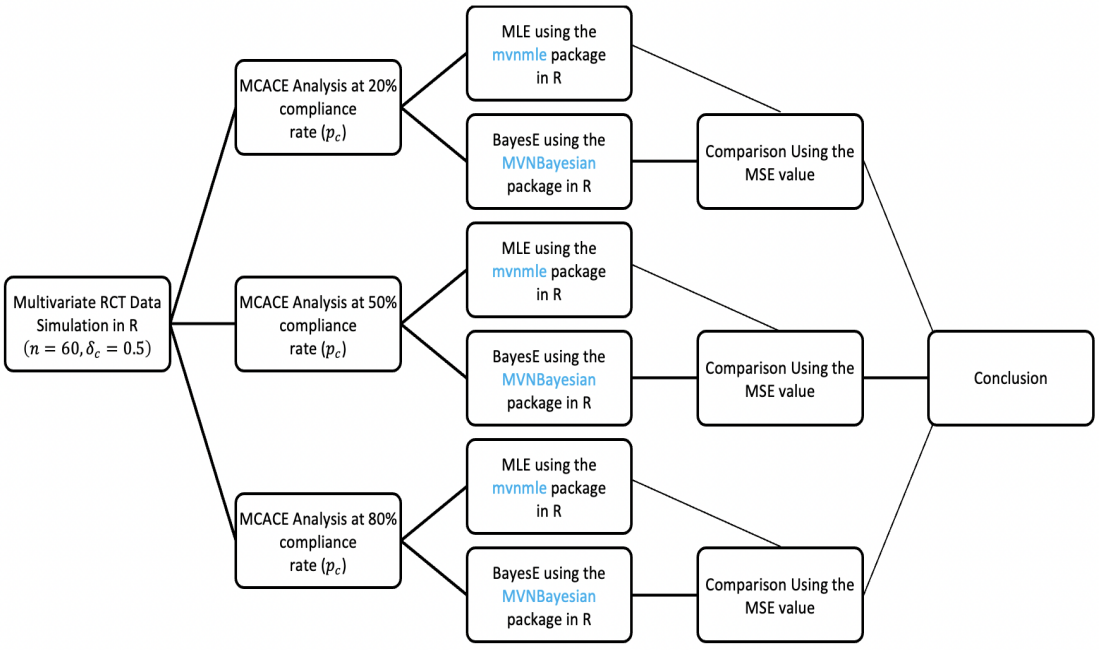

Figure 1. The Proposed Simulation Procedure

In this simulation study, we assume that the response or outcome Y follows a multivariate normal distribution, that is, $Y_{(t)} \sim MVN_k(\mu_c + \delta_c, \Sigma_c)$ for the treatment group and $Y_{(c)} \sim MVN_k(\mu_c, \Sigma_c)$ for the control group. For simplicity, compliance rate p_c is assumed to be unaffected by the baseline covariates and set to $20\%, 50\%$ and 80%. Also, the chosen sample size n for this study is 60 and the chosen treatment effect size δ_c is set to 0.5 because based on prior investigations, the combination $n = 60$ and $\delta_c = 0.5$ will produce precise estimates using the *MCACE* model via *MLE* [9]. Using this set-up, this paper will then investigate and compare the estimates derived via *BayesE*. Moreover, the limit number of iterations for the maximum likelihood estimation is set to 700 and the number of random vectors to be generated using *Gibbs Sampling* under the MVNBayesian package in R is set to 7000.

3 Results and Discussions

This section presents the derived *MCACE* estimates for both *Maximum Likelihood Estimation* (*MLE*) and *Bayesian* Estimation (*BayesE*). Let $\hat{\mu}_T$ be the treatment effect estimate derived via *MLE* and $\hat{\mu}_T^\star$ be the treatment effect estimate derived via *BayesE*. In this study, the sample size n is fixed at 60 and the effect size δ_c is fixed at 0.5. Comparison at varied values of the compliance rate $\rho_c \in \{20\%, 50\%, 80\%\}$ are investigated.

Table 1 gives the derived estimates $\hat{\mu}_T$ for the compliers in the treatment group via the *MLE* approach. Setting $\mu_c = (Y_1, Y_2, Y_3, Y_4, Y_5, Y_6)' = (1, 1, 1, 2, 2, 2)'$ as the true treatment effect before the start of the simulation process, we are interested in verifying the null hypothesis H_0 that μ_c is equal to the derived treatment effect estimate $\hat{\mu}_T$, that is,

$$H_0 : \mu_c = \hat{\mu}_T$$

at fixed $n = 60$ and $\delta_c = 0.5$ with different values of $\rho_c \in \{20\%, 50\%, 80\%\}$. This null hypothesis is rejected if $F > F_{df}^{\alpha}$ at a given level of significance α (say, $\alpha = 0.05$) and degrees of freedom df in favor of the alternative hypothesis written as:

$$H_1 : \mu_c \neq \hat{\mu}_T.$$

In particular, at $\rho = 50\%$, we see that

$$\hat{\mu}_T = (0.8038707, 0.9230134, 0.6898140, 1.2513369, 1.3259502, 1.2046297)'$$

and we want to know if this vector is significant different from $\mu_c = (1, 1, 1, 2, 2, 2)'$. The verification is assessed by performing the Hotelling's T^2 test by deriving an F-statistic. The computation is done by the R software and is summarized in Table 1.

Table 1. $\hat{\mu}_T$, estimates for μ_T derived via *MLE*

ρ_c	$\hat{\mu}_T$ values with fixed $\delta_c = 0.5$ and $n = 60$						Hotelling's T^2 Test (F-value)
	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	
20%	0.3049891	0.3095034	0.2925930	0.5193231	0.5334954	0.5593947	83.2028*
50%	0.8038707	0.9230134	0.6898140	1.2513369	1.3259502	1.2046297	10.8974*
80%	1.1641140	1.1769440	1.3644730	2.0181650	2.0981650	1.9477520	3.41035*
F_{crit}=2.1750 ($n = 60$), '$\star$' significant, 'ns' not significant							

For a given methodology to be efficient, the true parameter value should be close to the estimated value. Hence, in this analysis we want that the H_0 to be accepted. However, the Hotelling's T^2 test results show that when fixing n to 60, δ_c to 0.5, and varying ρ_c to 20%, 50%, and 60%, all the $\hat{\mu}_T$ are significantly different from $\mu_c = (1, 1, 1, 2, 2, 2)'$ so that $H_0 : \mu_c = \hat{\mu}_T$ is rejected. Therefore, there is a significant difference between the true treatment effect μ_c and $\hat{\mu}_T$, the estimated treatment effect derived via *MLE*, even at varying rates of compliance ρ_c. Nevertheless, it is worth noting that as ρ_c increases from 20% to 80%, the F-value of the Hotelling's T^2 test decreases at fixed $n = 60$ and $\delta_c = 0.5$. This means that the behavior of the derived $\hat{\mu}_T$ using *MLE* is possibly affected by the selection of the value of the compliance rate ρ_c. It may imply that at a larger value of ρ_c, the greater the chance H_0 will be accepted.

Similarly, we want to test that $H_0 : \mu_c = \hat{\mu}_T^\star$ versus $H_1 : \mu_c \neq \hat{\mu}_T^\star$ when deriving estimates via *BayesE*. Table 2 shows the derived values of $\hat{\mu}_T^\star$ at fixed $n = 60$ and $\delta_c = 0.5$. In particular, at $\rho = 80\%$ we see that

$$\hat{\mu}_T^\star = (1.1623530, 1.1673780, 1.3628940, 2.0037680, 2.0832860, 1.9612110)'$$

and we want to verify if this vector is not significantly different from $\mu_c = (1, 1, 1, 2, 2, 2)'$. However, results show that $H_0 : \mu_c = \hat{\mu}_T^\star$ is rejected in favor of $H_1 : \mu_c \neq \hat{\mu}_T^\star$. Similar conclusion and trend are observed for the estimates derived using *BayesE* as with estimates via *MLE* with respect to the values of the F-statistic when the compliance rate ρ_c increases from 20% to 80% at fixed sample size 60 and effect size 0.5.

Table 2. $\hat{\mu}_T^\star$, estimates for μ_T derived using *BayesE*

ρ_c	$\hat{\mu}_T^\star$ values with fixed $\delta_c = 0.5$ and $n = 60$						Hotelling's T^2 Test (F-value)
	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	
20%	0.3057378	0.3100779	0.2892077	0.5301085	0.5445906	0.5675145	$86.3412^\star$
50%	0.8022573	0.9181712	0.6835685	1.2801860	1.3443367	1.2354521	$13.3799^\star$
80%	1.1623530	1.1673780	1.3628940	2.0037680	2.0832860	1.9612110	$5.41676^\star$
F_{crit}=2.1750 (n=60), '$\star$' significant, 'ns' not significant							

Table 3. Comparison between $\hat{\mu}_T$ and $\hat{\mu}_T^\star$, estimates for μ_T

ρ_c	Estimates	$\hat{\mu}_T$ versus $\hat{\mu}_T^\star$ with fixed $\delta_c = 0.5$ and $n = 60$						F-test value
		Y1	Y2	Y3	Y4	Y5	Y6	
20%	MLE	0.3049891	0.3095034	0.2925930	0.5193231	0.5334954	0.5593947	0.0004^{ns}
	BayesE	0.3057378	0.3100779	0.2892077	0.5301085	0.5445906	0.5675145	
50%	MLE	0.8038707	0.9230134	0.6898140	1.2513369	1.3259502	1.2046297	0.0025^{ns}
	BayesE	0.8022573	0.9181712	0.6835685	1.2801860	1.3443367	1.2354521	
80%	MLE	1.1641140	1.1769440	1.3644730	2.0181650	2.0981650	1.9477520	0.0004^{ns}
	BayesE	1.1623530	1.1673780	1.3628940	2.0037680	2.0832860	1.9612110	
F_{crit}=2.1750 (n=60), '$\star$' significant, 'ns' not significant								

Next, we test whether the derived estimates via *MLE*, $\hat{\mu}_T$ is significantly different from $\hat{\mu}_T^\star$, estimates derived via *BayesE*. That is, we want to test the hypotheses $H_0 : \hat{\mu}_T = \hat{\mu}_T^\star$ versus $H_1 : \hat{\mu}_T \neq \hat{\mu}_T^\star$. Table 3 shows the result of the Hotelling's T^2 test with its corresponding F-values in comparing the estimates. Test result shows that H_0 is not rejected when fixing n to 60, δ_c to 0.5, and even if we vary the values of ρ_c. Nevertheless, it is observable that fixing ρ_c to 50%, the F-value for the Hotelling's T^2 test seems to be larger than the other values of the ρ_c. This means that the difference between the estimates is greatly affected by the compliance rate selection.

To show the advantage of the *BayesE* methodology over the *MLE* procedure, further test is conducted in this study. Figure 2 shows the plot of the estimated variances $\hat{\sigma}_T^2$ and $\hat{\sigma}_T^{2\star}$ derived from *MLE* and *BayesE*, respectively, when fixing n to 60, δ_c to 0.5, and varying ρ_c to 20%, 50%, and 80%. The variance (or precision) measures how close estimates from different samples are close to each other. The figure shows that the *BayesE* gave smaller estimated variance than when using the *MLE*. To further assess this claim, the Friedman's two-way analysis of variance is performed to see whether $H_0 : \hat{\sigma}_T^2 = \hat{\sigma}_T^{2\star}$ is rejected in favor of $H_1 : \hat{\sigma}_T^2 \neq \hat{\sigma}_T^{2\star}$.

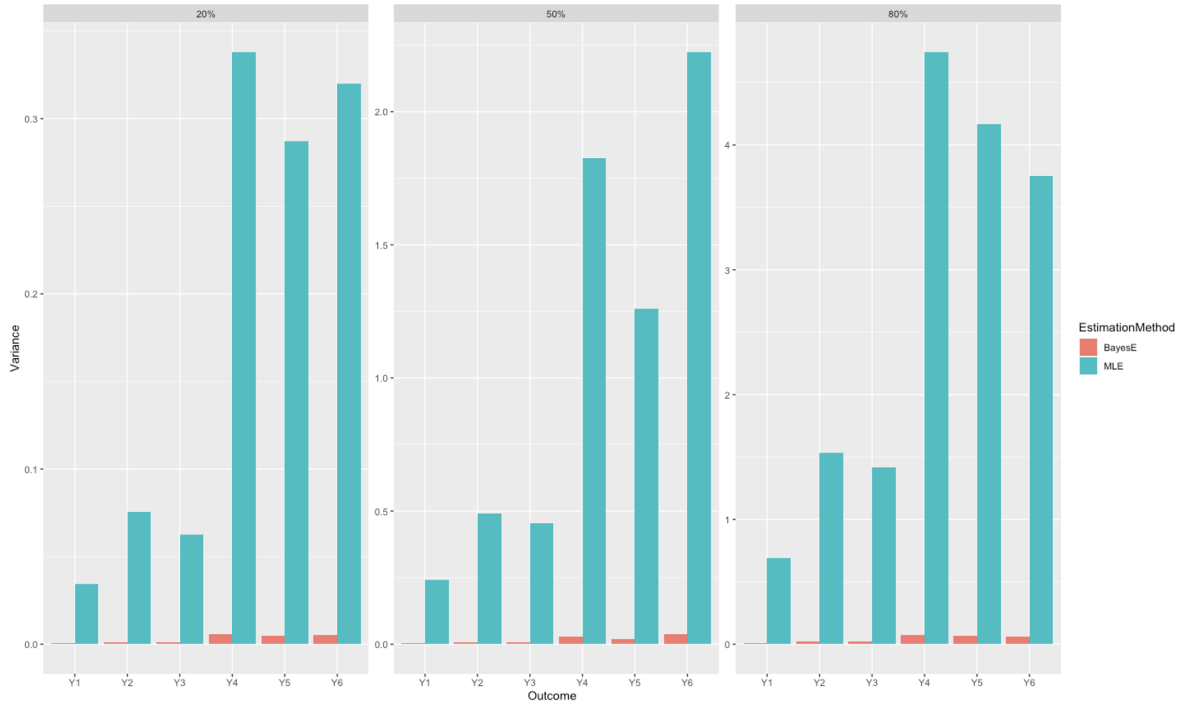

Figure 2. Plot of the Variance Estimates Derived Using *MLE* and BayesE

Table 4. Comparison Between $\hat{\sigma}_T^2 = Var(\hat{\mu}_T)$ and $\hat{\sigma}_T^{2\star} = Var(\hat{\mu}_T^{\star})$

ρ_c	Estimates	$\hat{\sigma}_T^2$ versus $\hat{\sigma}_T^{2\star}$ with fixed $\delta_c = 0.5$ and $n = 60$						Friedman's
		Y1	Y2	Y3	Y4	Y5	Y6	
20%	MLE	0.0343015	0.0753319	0.0627598	0.3379417	0.2873491	0.3198210	0.0143*
	BayesE	0.0005282	0.0011979	0.0009985	0.0056671	0.0047312	0.0050955	
50%	MLE	0.2406664	0.4901848	0.4555062	1.8260157	1.2612716	2.2233802	0.0143*
	BayesE	0.0038647	0.0079181	0.0073015	0.0301057	0.0208570	0.0371463	
80%	MLE	0.6881509	1.5361308	1.4173610	4.7430452	4.1664471	3.7489259	0.0143*
	BayesE	0.0107163	0.0242434	0.0237186	0.0748502	0.0660305	0.0585237	
significance codes '$\star\star\star$' 0; '$\star\star$' 0.001; '$\star$' 0.01; '.' 0.05								

Table 4 shows the result of the Friedman's Two-way ANOVA test for the comparisons between $\hat{\sigma}_T^2$ using *MLE* and $\hat{\sigma}_T^{2\star}$ using *BayesE* at $n = 60$, $\delta_c = 0.5$, and varying the values of ρ_c. The test result shows that there is enough evidence to reject $H_0 : \hat{\sigma}_T^2 = \hat{\sigma}_T^{2\star}$ and conclude that there is a significant difference between the variances of the estimates, $\hat{\sigma}_T^2$ and $\hat{\sigma}_T^{2\star}$.

Further, doing a one-sided test, that is, with an alternative hypothesis $H_2 : \hat{\sigma}_T^2 > \hat{\sigma}_T^{2\star}$, the result shows that, on the average, $\hat{\sigma}_T^{2\star}$ has significantly smaller values than that of $\hat{\sigma}_T^2$ at a level of significance of $\alpha = 0.05$. In conclusion, the *MCACE* analysis using *BayesE* produced smaller variances of the estimates and thus, estimates produced by the said methodology are more precise than those estimates produced by *MCACE* via *MLE* at fixed $n = 60$ and $\delta_c = 0.5$ with varying values of ρ_c.

Further analysis is done to check the accuracy of the estimates. Table 5 shows the comparison of the *Mean Squared Error (MSE)* values for the estimates derived from both *MLE* and *BayesE* methodologies. The *MSE* measures the accuracy of an estimator, that is, it measures how close the estimate is to the true treatment effect value. It can be observed from Table 5 that the

derived *MCACE* estimates using *BayesE* gave smaller *MSE* values than those derived using *MLE* regardless of the compliance rate values at fixed sample size $n = 60$ and effect size $\delta_c = 0.5$. Also, we see that as the compliance rate increases, the *MSE* values also increases. This means that the proposed *MCACE* models using *BayesE* gave more accurate and consistent treatment effect estimates than the existing *MCACE* models using *MLE*.

Table 5. Comparison Between the MSE of $\hat{\mu}_T$ and $\hat{\mu}_T^{\star}$, estimates of μ_T

ρ_c	Estimates	*MSE* values with fixed $\delta_c = 0.5$ and $n = 60$						Ave. MSE
		Y1	Y2	Y3	Y4	Y5	Y6	
20%	MLE	0.0343015	0.0753319	0.0627598	0.3379417	0.2873491	0.3198211	0.1862508
	BayesE	0.0005390	0.0012013	0.0010122	0.0056749	0.0047923	0.0050958	0.0030525
50%	MLE	0.2406664	0.4901848	0.4555062	1.8260157	1.2612716	2.2233802	1.0828374
	BayesE	0.0038873	0.0079267	0.0073139	0.0302766	0.0208688	0.0371633	0.0179061
80%	MLE	0.6881509	1.5361308	1.4173610	4.7430452	4.1664471	3.7489259	2.7166768
	BayesE	0.0107240	0.0243162	0.0237218	0.0781854	0.0675934	0.0585465	0.0438478

4 Conclusions and Recommendations

For this study, with the assumption that the response Y follows a multivariate normal distribution, it is shown that for $n = 60$, $\delta_c = 0.5$ and $\rho_c \in \{20\%, 50\%, 80\%\}$, the *MCACE* analysis using *BayesE* gave more precise treatment effect estimates than the existing *MCACE* analysis using *MLE* based on their respective variance values of the estimate. Furthermore, the proposed *MCACE* models via *Bayesian* estimation gave smaller *MSE* values than the *MCACE* models derived via *MLE*. It is more likely that the proposed *MCACE* analysis using *BayesE* outperformed the existing *MCACE* analysis using *MLE* when it comes to giving more accurate and consistent estimates subject to the conditions set for the simulation study.

The *Multivariate CACE* (*MCACE*) model proposed in this paper is rather a basic one, for it ignores the effects of the baseline covariates on the response or outcome variable. Further improvements could be made to the *MCACE* model to provide the most accurate and precise analysis results by considering the baseline characteristics. We assumed the outcome Y to follow a multivariate normal distribution. In fact, in a *RCT* set-up, outcome does not always follow an exact multivariate normal distribution, which may violate the assumptions of the likelihood function. For future studies in this research direction, the researchers recommend a nonparametric model to deal with the non-normal outcomes. Also, it is recommended that research be done with real or raw randomized controlled trial datasets and methodologies on how to to go about with the analysis using *MCACE* models when there are possible outliers and missing observations in the dataset.

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References

[1] Gelman, A., Hwang, J. and Vehtari. *A. Understanding predictive information criteria for Bayesian models.* Stat Comput 24, 2014, 997–1016.

[2] Gentle, J. E. Computational Statistics. Statistics and Computing. New York: Springer, 2009, pp. 315–316.

[3] Knox, C. R., Lall, R., Hansen, Z., and Lamb, S.E. *Treatment compliance and effectiveness of a cognitive behavioural intervention for low back pain: a complier average causal effect approach to the best data set.* BMC Musculoskeletal Disorders, 2014, 15(1): 17–27.

[4] Laird, N. M. and Ware, J. H. *Random-effects models for longitudinal data.* Biometrics, 1982, 38(4):963–974.

[5] Lavrakas, P. Encyclopedia of Survey Research Methods, 2008.

[6] Liang KY and Zeger SL. *Longitudinal data analysis using generalized linear models.* Biometrika. 1986, 73(1):13–22.

[7] Linda H. Y. Yaua, Roderick J. Little et al. *Inference for the complier-average causal effect from longitudinal data subject to noncompliance and missing data, with application to a job training assessment for the unemployed.* 2011. 96:456, 1232-1244.

[8] Sheiner L.B. and Rubin, D.B. *Intention-to-treat analysis and the goals of clinical trials.* Clinical Pharmacology and Therapeutics, 1995, 57(1):6–15.

[9] Yue Ma et. al. *Multivariate CACE Analysis with an Application to Arthritis Health Journal Study*, Simon Fraser University. Summer 2018. .